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The impact of the COVID-19 pandemic on the course of miscarriages

Marta Kacprzak[1], Hanna Moczulska[2], Katarzyna Ploszka[3], Marta Chrzanowska-Steglinska[1], Piotr Sieroszewski[1]

[1]*Department of Fetal Medicine and Gynaecology, Medical University of Lodz, Poland*
[2]*Department of Clinical Genetics, Medical University of Lodz, Poland*
[3]*Department of Biostatistics and Translational Medicine, Medical University of Lodz, Poland*

ABSTRACT

Objectives: Miscarriage is the most common complication of pregnancy. Infections are well-known causes of pregnancy loss. It has been suggested that infection with SARS-CoV-2 virus may also have an adverse effect on the course of early pregnancy, causing miscarriage.

Aim: To assess the impact of the COVID-19 pandemic on pregnancy loss during the first half of pregnancy.

Material and methods: The clinical records of patients hospitalized at the Department of Fetal Medicine and Gynecology; Medical University of Lodz were retrospectively reviewed. The study was done during the pandemic (March 2020 to the end of March 2022) and the previous 2 years due to missed abortion, indicated by no fetal heartbeat and spontaneous (complete or incomplete) abortion with vaginal bleeding.

Results: While 682 women were hospitalized due to miscarriage in the first half of pregnancy in the period 2018–2020, there were 516 hospitalized during the pandemic. No differences in the proportion of missed and spontaneous abortions with bleeding were found between the group of patients before and during the epidemic SARS CoV-2. COVID-19 exposure appears to have an impact on earlier pregnancy loss.

Conclusions: There is no evidence that the COVID-19 pandemic predisposes to the abnormal course of pregnancy in its first half.

Keywords: COVID-19; pandemic; miscarriages

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INTRODUCTION

The COVID-19 outbreak was first detected in Wuhan, China in November 2019. The following epidemic, which began in the Chinese province of Hubei, eventually assumed the proportions of a pandemic. Its causative agent, the SARS-Cov-2 virus, is a single-stranded RNA member of the coronaviridae. It has been shown to be very similar to other highly pathogenic coronaviruses, such as Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) [1–3].

On 4 March, 2020, the first case of SARS-Cov-2 infection was detected in Poland, where COVID-19 infection has been confirmed in over six million inhabitants. The course of the infection is diverse and difficult to predict, ranging from completely asymptomatic to severe pneumonia with respiratory distress syndrome or multiple organ failure.

One of the risk factors for severe COVID-19 infection is pregnancy. Also, it has been proposed that infection with SARS-CoV-2 virus may have an adverse effect on the course of pregnancy, causing miscarriage.

Corresponding author:
Marta Kacprzak
Department of Fetal Medicine and Gynaecology, the Medical University of Lodz, Poland
e-mail: kacprzak-marta@wp.pl

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Miscarriage, or loss of pregnancy before week 22, is the most common complication of pregnancy. Loss of pregnancy is referred to as early miscarriage if occurring in the first trimester, and late miscarriage after 12 weeks of pregnancy. It is estimated that around 15% of clinically confirmed pregnancies are miscarried; however, the actual percentage may be higher. It is estimated that about 30% of embryos do not implant, and that another 30% are lost before the next menstrual period, in cases where pregnancy is confirmed only based on the concentration of human chorionic gonadotropin [4].

In most cases, the causes of miscarriage are difficult to identify; however, infections are known to result in pregnancy loss. To ensure the proper course of pregnancy, the immune system of the pregnant women maintains a balance between tolerance and rejection of the alloantigens (paternal) of the developing embryo, and later the fetus. Any infection can upset this balance, resulting in the loss of pregnancy [5, 6].

The SARS-Cov-2 virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor, thus enabling its entry into target cells. Although ACE2 is particularly prevalent in type II pneumocytes, it has also been found in the upper respiratory tract, including the throat, and in the gastrointestinal tract, mainly in the small intestine [7]. In addition, ACE2 has been identified at different levels in the heart, liver, kidneys and the brain, as well as in endometrial cells, embryonic cells and placental cells (*e.g.*, syncytio- and cytotrophoblast) [8–11]. The expression of ACE2 is negatively correlated with gestational age: it is highest in trophoblast cells during the first trimester, and insignificant or undetectable in placenta cells during the third trimester [12].

Vertical transmission of the infection, especially during organogenesis, may have a very negative influence on the further course of pregnancy. In particular, the pathogens from the TORCH group (*Toxoplasma*, other, *Rubella*, cytomegalovirus, *Herpes*) have been associated with obstetric failures in pregnant woman [6, 13].

Key complications observed among patients with COVID-19 infection are coagulation disorders. Up to 46% of patients with laboratory-confirmed SARS-CoV-2 infection have abnormal high D-dimer values (≥ 0.5 mg/L). [14] Both congenital and acquired thrombophilia are known to result in *inter alia* miscarriage, premature placental abruption and preeclampsia [15, 16].

Thus, the question arises as to whether the SARS-CoV-2 virus may influence the risk of miscarriage.

The aim of the study was to determine whether the COVID-19 pandemic was associated with an increase in miscarriage rate.

MATERIAL AND METHODS

A review was performed of the clinical records of patients admitted to the Department of Fetal Medicine and Gynecology of the Medical University of Lodz in 2018–2022 for miscarriage. All patients had reported a spontaneous abortion with complete or incomplete vaginal bleeding or a missed abortion, in the first 22 weeks of pregnancy, confirmed by two ultrasound examinations. The case group comprised women aged 17–46 admitted to the Clinic during the SARS-CoV-2 coronavirus pandemic from March 2020 to the end of March 2022. The control group included patients aged 16–48 years admitted in the same period before the pandemic in 2018–2020. A total of 1,198 patients were enrolled in the study: 682 controls, *i.e.*, hospitalized before the pandemic, and 516 cases, *i.e.*, hospitalized during the pandemic.

Among the 516 women hospitalized for an abnormal course of early pregnancy during the early part of the COVID-19 pandemic, *i.e.*, between March and July 2020, 91 did not have a PCR test for COVID-19 infection.

Since July 2020, all patients admitted for elective or emergency procedures have received a routine PCR test for COVID-19. Among the study group, the result was positive in 26 patients, and negative in 399. In the infected patients, the course of infection was mild.

Ninety-one patients without the PCR test for COVID-19 were excluded from statistical analysis (Fig. 1).

Statistical analysis

For nominal variables, 2 × 2 tables with frequencies and percentages were used, and the Chi^2 test with appropriate corrections was used to assess differences between the study groups. Continuous variables with a non-normal

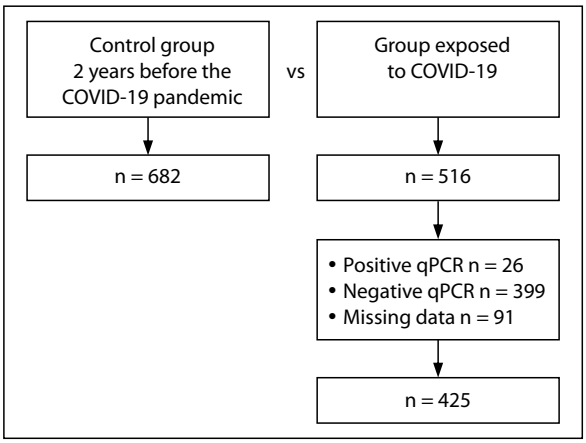

Figure 1. Flowchart of the two cohorts

Table 1. Differences between the women exposed to COVID-19 and the control group

	Median (Q1–Q3)/n%		
	Control group (n = 682)	**Group exposed to COVID-19 (n = 425)**	**p**
Age [years]	32 (28–37); min–max: 16–48	32 (28–37); min–max: 18–46	0.618
Number of pregnacies	2 (1–3); min–max: 1–7	2 (1–3); min–max: 1–8	0.197
Number offspring	1 (0–10); min–max: 0–6	1 (0–1); min–max: 0–6	0.500
Gestational week at pregnancy loss	9 (7–10); min–max: 5–20	8 (6–10); min–max: 5–22	**< 0.001**
Spontaneous abortion	254 (37.24%)	156 (36.71%)	0.857
Missed abortion	428 (62.76%)	269 (63.29%)	

distribution based on the Shapiro–Wilk W test result, as well as ordinal variables, were characterized using the median with 25% and 75% quartiles (Q1–Q3). The non-parametric Mann–Whitney U test was used to assess the differences between continuous and ordinal variables. Statistically significant results were presented using a box-whisker plot. Then, Kaplan–Meier curves together with the log-rank test were used to assess the time to the event. Statistical significance for all analyzes was $p < 0.05$.

Statistical tests were performed using the STATISTICA software version 13.3 (StatSoft TIBCO 2023).

RESULTS

Table 1 presents the most important differences between the groups. No statistically significant differences were found between the age of patients admitted with miscarriages in the groups before and during the SARS-CoV-2 pandemic. The median age in both groups was 32 years ($p = 0.62$).

In addition, no significant difference was found between the groups regarding the parity, previous abortion and the number of offspring (Supplemental Tab. S1).

Among the patients in the control, *i.e.*, pre-pandemic, group admitted to the clinic, 428 presented with a missed abortion, and 254 with complete or incomplete spontaneous abortion. In comparison, during the pandemic period, the respective values were 269 and 156. However, no differences were found in the proportion of missed to spontaneous abortions between the pre-pandemic and pandemic groups.

The survival analysis (Fig. 2) showed that patients exposed to COVID-19 were statistically significantly ($p < 0.002$) predisposed to miscarriage much earlier (8 weeks of gestation) compared to women admitted to the clinic in the same period before the pandemic (9 weeks of gestation).

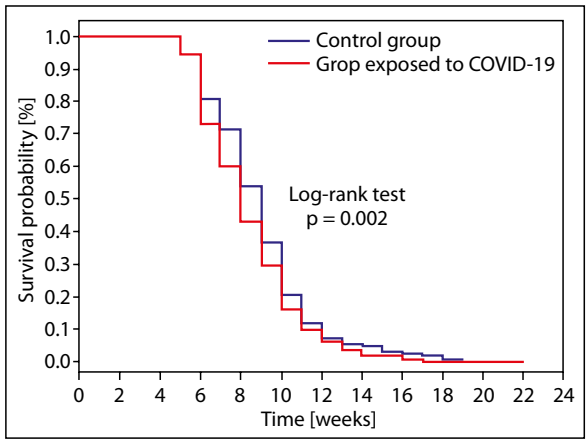

Figure 2. Survival analysis — Kaplan–Meier curves and log-rank test. Patients exposed to COVID-19 miscarry earlier than controls

DISCUSSION

COVID-19 follows a similar course of infection in pregnant women and non-pregnant adults. As many as 40–45% of cases are asymptomatic, and only 10–20% of those infected have a severe course of the disease [17]. In addition, there appears to be little difference during pneumonia arising in the course of SARS-CoV-2 infection in pregnant women and that observed in the general population [18]. Furthermore, a severe course of the infection does not appear to increase the risk of miscarriage or premature birth [19].

One study performed in a hospital in Turin, Italy compared cases of COVID-19 infection occurring among 100 women with spontaneous abortion during the first trimester of pregnancy, with 125 pregnant women with a normal pregnancy. Examination of nasopharyngeal swab samples, and COVID-19 IgG and IgM antibody levels in blood samples, found that SARS-CoV-2 virus infection does not seem to increase the risk of early pregnancy loss [20]. Similar results were obtained regarding SARS-CoV-2 seroprevalence among women with miscarriages in the first half of pregnancy and women with a proper course of pregnancy [21].

In a Danish study, la Cour Freiesleben et al. [22] assessed the effect of SARS-CoV-2 infection based on the presence of SARS-CoV-2 virus IgG and IgM antibodies, on the double test result and the course of the first trimester

of pregnancy. It was found that in pregnant women, the presence of antibodies was not related to any increase in nuchal translucency (NT) thickness, or the concentration of PAPP-A or beta-hCG protein. In addition, it did not increase the risk of miscarriage in the compared groups of pregnant women with and without SARS-CoV-2 virus IgG and IgM antibodies [22].

A study in Montreal investigated the impact of the pandemic environment as a stress-increasing factor on the risk of miscarriage in the first trimester of pregnancy [23]. Contrary to previous observations regarding conditions of increased stress, the pandemic environment did not seem to be an independent predictor of early pregnancy loss among the studied population of women [24, 25].

However, in a study of the Polish population, 22% of respondents admitted that the pandemic influenced their decisions to postpone having children. More specifically, they reported significant concerns about access to health care and the unstable economic situation resulting from the pandemic [26]. These findings are in line with preliminary data of the Polish Central Statistical Office indicating that there were approximately 15% fewer live births in in Poland in 2021 than in 2018.

Isolation intended to limit the spread of other infectious diseases was also an important factor influencing the total number of miscarriages related to infectious agents. Higher failure rates in early pregnancy are typically recorded during the flu season [27]. Limiting interpersonal contacts, wearing masks and ensuring proper hygiene appear to be advisable during early pregnancy.

However, the question of whether the pandemic influences reproduction and the course of early pregnancy remains ambiguous. Even so, it seems that neither COVID-19 infection nor the increased levels of stress associated with the pandemic environment increase the incidence of loss in the first half of pregnancy, and isolation may have a protective effect. However, a lower overall number of miscarriages was noted in the first half of pregnancy in the present study, but this could have resulted primarily from a lower total number of pregnancies, which was very likely related to postponing the decision to have children.

CONCLUSIONS

1. The data indicates that miscarriages in exposed to COVID-19 women are significant earlier than patients without COVID-19 exposure. However, no increase in the number of pregnancy loss in the first half of pregnancy was observed during the pandemic period from March 2020 to the end of March 2022.
2. Although COVID-19 infection was not found to have any effect on miscarriages in the first half of pregnancy, it was not possible to perform a statistical analysis on this data due to the small number of SARS-CoV-2 positive patients.
3. The COVID-19 pandemic had a negative impact on the reproductive decisions of couples due to concerns about possible complications during pregnancy for both mother and child.

Article information and declarations

Conflict of interest

All authors declare no conflict of interest.

Supplementary material

Table S1 and Figure S1.

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SUPPLEMENTARY MATERIALS

Table S1. Total number of miscarriages, after rejection of 91 patients with missing data

Variable		n (%)	
		Group exposed to COVID-19 (n = 425)	Control group (n = 682)
Total number of miscarriages	1	292 (68.71%)	494 (72.43%)
	2	85 (20.00%)	134 (19.65%)
	3	39 (9.18%)	42 (6.16%)
	4	7 (1.65%)	9 (1.32%)
	5	2 (0.47%)	3 (0.44%)

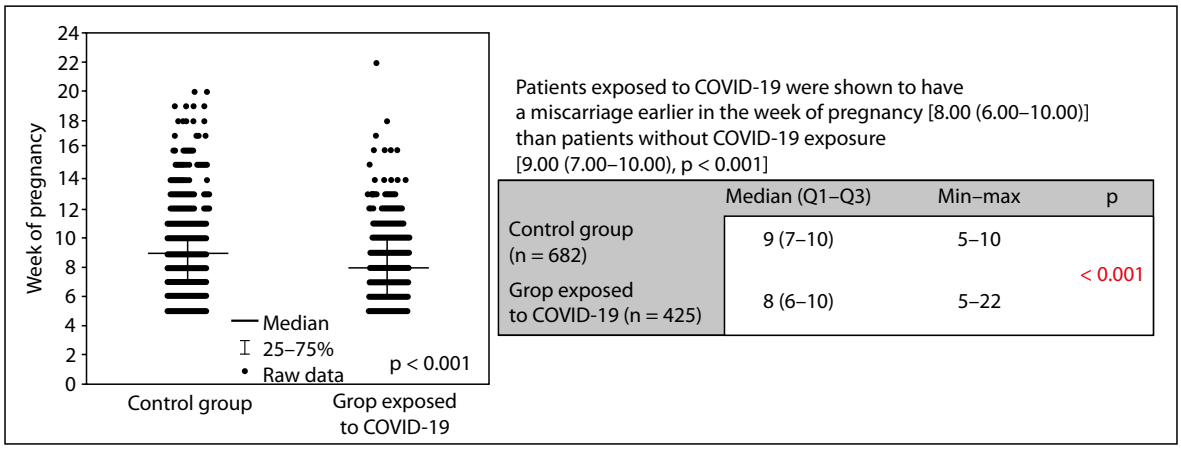

Figure S1. Exposure to COVID-19 and the week of miscarriage